REMARKS

The foregoing amendment is filed in response to the January 13, 2004, Office Action (Office Action). Upon entry of the foregoing amendment:

The Title is replaced with a new Title.

Claim 42 is herein amended. Support for the amendments can be found throughout the specification, and specifically at page 61, first paragraph and in originally filed claims 42 and 45.

Claims 1-31 and 53-90 stand withdrawn as being drawn to a non-elected invention.

Claims 32-41 and 43-52 are herein canceled.

Claims 91-96 are newly added. Support for the added claims can be found throughout the specification, and specifically at page 61, paragraph 2.

Claims 42 and 91-96 are pending in the application.

I. Restriction Requirement

Applicants gratefully acknowledge the reconsideration of restriction between Groups V and VI. It is understood that Groups V and VI will be examined together.

Applicants also acknowledge their election of SEQ ID No. 6, with traverse.

Applicants maintain their traversal of the final restriction requirement between SEQ ID NOs 3, 6, 13 and 14. Applicants respectfully submit that the Patent Office has not met its burden of showing that a full search of the SEQ IDs would be unduly burdensome. Although Applicants agree that a teaching that would anticipate one claimed sequence would not necessarily anticipate or render obvious another claimed sequence, Applicants submit that it would not be unduly burdensome for the Office to perform a computer search of each of four independent and distinct sequences. Applicants submit that this is especially the case where, as here, there are other claim elements that the Office could use to focus the search, thereby further limiting the

scope of the search, and permitting inclusion of a greater number of independent and distinct sequences within the search strategy. Accordingly, Applicants respectfully request reconsideration and withdrawal of the restriction between SEQ ID NOs 3, 6, 13 and 14. In any case, Applicants request that the restriction between SEQ ID NOs 3, 6, 13 and 14 be held in abeyance until allowable subject matter is identified.

II. Formal Matters:

The Office Action objected to the Title as not being descriptive of the claimed subject matter. By the foregoing amendment, the original title has been changed to "Method for Identifying Prokineticin Receptor Ligands." Applicants respectfully submit that this amendment is sufficient to overcome the objection, and request withdrawal of the objection in view thereof.

Applicants acknowledge the objection to claim 48 as being drawn in part to non-elected SEQ ID 3. By the foregoing amendment, claim 48 has been canceled. Accordingly, this specific objection is moot. To the degree that this objection may apply to any of the pending claims, it is noted that Applicants have requested reconsideration of the restriction requirement. Applicants further request that this objection be held in abeyance until such time as allowable subject matter is identified.

Claims 36, 39, 44 and 50 have been objected to for reciting the M2A7 cell line. By the foregoing amendment, these claims have been canceled, rendering this specific objection moot. To the extent that this objection may apply to any pending claims, Applicants offer these remarks: Applicants understand that this is an objection, rather than a rejection for lack of enablement. Applicants agree with the statement in the Office Action that the cell line is known in the art, and it readily available to the public. Accordingly, Applicants submit that a deposit is not necessary in this case. Accordingly, Applicants request that this objection be withdrawn.

III. § 112, Second Paragraph Rejection

Claims 33-52 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. By the foregoing amendment, claims 33, 37, 41, 46, 47 and 52 have been canceled, rendering this ground of rejection moot. To the extent that this rejection might be applied against the pending claims, Applicants point out that the claims have been amended to positively recite method steps, which clearly indicate how a candidate compound is identified as a prokineticin ligand. Accordingly, Applicants respectfully request withdrawal of the rejection under §112, second paragraph.

IV. § 102(e) Rejection

Claims 33, 34, 37, 41, 42, 46-48 and 52 stand rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Sheppard et al., U.S. Patent No. 6,485,938 (Sheppard). Applicants respectfully traverse this rejection.

By the foregoing amendment, claims 33, 34, 41, 46-48 and 52 have been canceled, rendering this rejection moot in regard to these claims.

Claim 42 has been amended to recite contacting a preparation comprising a prokineticin receptor and calcium ion indicator with one or more candidate compounds, which is not taught by Sheppard. Accordingly, Applicants submit that claim 42 is not anticipated by Sheppard.

As Sheppard fails to teach each element of claim 42, Applicants submit that the rejection under § 102(e) over Sheppard is untenable and should be withdrawn.

Applicants submit that claims 91-96 are also not anticipated by Sheppard. Claims 91-96 depend, directly or indirectly, from claim 42. As each of these claims are at least as limiting as claim 42, the same reasoning that applies to claim 42 also applies to claims 91-96. Accordingly, Applicants submit that a rejection of claims 42 and 91-96 under § 102(e) over Sheppard would be untenable.

V. § 103(a) Rejection

Claims 35, 38, 43 and 49 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Sheppard. Applicants respectfully traverse this rejection.

By the foregoing amendment, claims 35, 38, 43 and 49 have been canceled, thereby rendering the rejection moot with respect to these claims. To the extent that the rejection might be applied against the pending claims, Applicants submit that such a rejection would be untenable.

In order for a single reference to render a claim obvious, it must teach or fairly suggest each element of the claim to the person having ordinary skill in the art. The reference must provide motivation to modify the reference to arrive at the claimed subject matter as a whole. See MPEP § 2142. Applicants submit that the *prima facie* case of obviousness has not been established.

As best understood by Applicants' counsel, the Office Action states that Sheppard fails to teach monitoring of calcium mobilization as a means of detecting ligand-receptor binding, but that the claimed method would nonetheless have been obvious because Sheppard teaches that Zven-Zven Receptor binding gives rise to Ca^{++} mobilization and one of ordinary skill in the art would have known how to measure calcium ion mobilization. Applicants respectfully disagree with this conclusion.

Applicants agree with the Office Action that Sheppard fails to explicitly teach the claimed method of identifying a prokineticin receptor ligand, comprising the steps of: contacting a preparation comprising a prokineticin receptor and calcium ion indicator with one or more candidate compounds, and measuring a calcium ion indicator signal, whereby a compound that mobilizes calcium ion is identified as a prokineticin receptor ligand. Additionally, Applicants submit that Sheppard fails to suggest such a method, because one of ordinary skill in the art would not have known from reading Sheppard that Zven-Zven receptor binding gives rise to

calcium ion mobilization, and thus would not have been motivated to practice the claimed invention.

In particular, the Office Action points to Sheppard column 10, lines 54-63, as providing teaching of measuring calcium ion mobilization to identify Zven receptor ligands. Applicants respectfully disagree with the Office Action's interpretation of this passage. Sheppard does not state that any one of the metabolic events recited in lines 54-63, let alone calcium mobilization, arises from Zven-Zven receptor binding. What Sheppard teaches in this passage is that several metabolic events may arise from receptor binding, and that some metabolic events that often arise from ligand receptor binding include gene transcription, phosphorylation, dephosphorylation, increases in cyclic AMP production, mobilization of cellular calcium, mobilization of membrane lipids, cell adhesion, hydrolysis of inositol lipids and hydrolysis of phospholipids. Sheppard does not teach which, if any, of these disparate, and in some cases contradictory, metabolic events arise from Zven-Zven receptor interactions. Thus, one of ordinary skill in the art would not known to measure Zven ligand-Zven receptor binding by the claimed method.

The person having skill in the art would read the teaching of Sheppard as being broad enough to cover many different hypotheses of Zven's (prokineticin's) mode of action. Whereas calcium mobilization is one of the mechanisms that stimulates the contraction of gastrointestinal smooth muscle, at the time that Sheppard filed his patent application ample evidence existed supporting other signaling pathways. For instance, inhibition of inhibitory potassium and chloride channels were also know to lead to contraction of gastrointestinal smooth muscle (Horowitz et al.[1], 2000, page 27-37; Vogalis[2], 2000). It was also known that a variety of potassium channel blocking drugs could dramatically affect the activity of gastrointestinal smooth muscle. Indeed, at the time of Sheppard's filing, one of the particularly likely families of

[1] Horowitz, B, Ward SM, and Sanders KM. Cellular and molecular basis for electrical rhythmicity in gastrointestinal muscles. Annu Rev Physiol 61: 19-43, 1999. See attached IDS.
[2] Vogalis F. Potassium channels in gastrointestinal smooth muscle. J Auton Pharmacol. 2000 Aug;20(4):207-19. See attached IDS.

mediators was thought to be the voltage-gated potassium channels Kv (Farrugia[3], 1999). A number of members of this Kv family have been directly cloned from gastrointestinal tract (Hart[4] et al., 1993; Chandy & Gutman[5], 1995; Schmalz et al.[6], 1998). Compounds such as phorbol dibutyrate and excitatory neurotransmitter acetylcholine have been shown to contract gastrointestinal smooth muscle via inhibiting Kv currents (Vogalis et al.[7], 1995).

In fact, after Schweitz et al.[8] examined the contractile effect of MIT1, the snake homologue of mammalian PKs, on the gastrointestinal smooth muscle, they actually concluded that "the site through which MIT1 exerts its action might be a potassium channel....The putative potassium conductance involved in MIT1 action would be a potassium channel with a very high affinity for the toxin [MIT1]" (last paragraph of Schweitz et al.) Given the large number of possible modes of action for prokineticins, the person having ordinary skill in the art would not have been taught by Sheppard that prokineticin receptor ligands could be identified by measuring calcium mobilization.

Applicants were the first to have demonstrated that calcium mobilization is responsible for the contractile effect of prokineticins on isolated ileal segments (present application and Li et al.[9], 2001), and thus is the signaling pathway for prokineticin receptor. This was not taught by Sheppard, whose shotgun disclosure covered multiple, contradictory modes of prokineticin

---

[3] Farrugia, G. Ionic conductances in gastrointestinal smooth muscles and interstitial cells of Cajal. Annu Rev Physiol 61: 45-84, 1999. See attached IDS.
[4] Hart PJ, Overturf KE, Russell SN, Carl A, Hume JR, Sanders KM, Horowitz B. Cloning and expression of a Kv1.2 class delayed rectifier K+ channel from canine colonic smooth muscle. Proc Natl Acad Sci U S A. 1993 Oct 15;90(20):9659-63. See attached IDS.
[5] Chandy KG, Gutman GA. 1995. Voltage-gated K+ channel genes. In Ligand and Voltage-Gated Ion Channels, ed. A North, pp. 1-71. Boca Raton, FL: CRC See attached IDS.
[6] Schmalz F, Kinsella JL, Koh SD, Vogalis F, Schneider A, Flynn ERM, et al. 1998. Molecular identification of a component of delayed rectifier current in gastrointestinal smooth muscles. Am. J. Physiol. 274:G901-11. See attached IDS.
[7] Vogalis F, Ward M, Horowitz B. 1995. Suppression of two cloned smooth muscle-derived delayed rectifier potassium channels by cholinergic agonists and phorbol esters. Mol. Pharmacol. 48:1015-23. See attached IDS.
[8] Schweitz H, Pacaud P, Diochot S, Moinier D, Lazdunski M. MIT(1), a black mamba toxin with a new and highly potent activity on intestinal contraction. FEBS Lett. 1999 Nov 19;461(3):183-8. See previously submitted IDS.
[9] Li M, Bullock CM, Knauer DJ, Ehlert FJ, Zhou QY. Identification of two prokineticin DNAs: recombinant proteins potently contract gastrointestinal smooth muscle. Mol Pharmacol. 2001 Apr;59(4):692-8. See previously submitted IDS.

action. In particular, Applicants demonstrated that prokineticin receptors are found directly in the cell membrane of gastrointestinal smooth muscle, as tetrodotoxin, which would inhibit the release of other excitatory mediator, did not block the contractile effect of PK1 on gastrointestinal smooth muscle. Applicants further demonstrated that calcium is a downstream mediator of PK1's (prokineticin 1's) contractile effect of gastrointestinal smooth muscle, as calcium chelating EGTA and calcium channel blocker verapamil and nifedipine blocked PK1's contractile effect.

Given the state of the art at the time that the present inventors invented the claimed methods, the person of ordinary skill in the art would have envisioned multiple possible metabolic consequences of Zven-Zven receptor binding that might give rise to a cognizable signal. A person having ordinary skill in the art would have been just as likely to be led by Sheppard to look for potassium or chloride ion channel activity, or some other metabolically significant activity, as a consequence of Zven-Zven receptor binding.

In view of the foregoing, Applicants submit that a rejection of the pending claims under U.S.C. § 103(a) over Sheppard alone would be untenable and should be withdrawn.

Claims 40, 45 and 51 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Sheppard in view of Costanzo. Applicants respectfully traverse this rejection.

By the foregoing amendment, claims 40, 45 and 51 have been canceled. Thus, the rejection is moot with respect to claims 40, 45 and 51.

As previously noted, claim 42 has been amended to include the limitations of originally presented claim 45, and claims 91-96 depend from claim 42. Applicants submit that the § 103(a) rejection over Sheppard in view of Costanzo is untenable with respect to all the pending claims.

Claim 42 is drawn to a method of identifying a prokineticin receptor ligand, comprising the steps of: contacting a preparation comprising a prokineticin receptor and calcium ion indicator with one or more candidate compounds, and measuring a calcium ion indicator signal, whereby a compound that mobilizes calcium ion is identified as a prokineticin receptor ligand.

As best understood by Applicants' counsel, the Office Action acknowledges that Sheppard fails to teach monitoring calcium ion mobilization. However, the Office Action avers that Sheppard teaches calcium mobilization as a result of receptor-ligand interaction. The Office Action then provides Costanzo as a secondary reference to provide the missing teaching of monitoring calcium influx as a means of detecting ligand-receptor binding. Applicants submit that the Office Action fails to establish a proper *prima facie* case of obviousness because the combination of references fails to teach the person having ordinary skill in the art each element of the claimed invention.

As discussed above, Sheppard fails to teach that Zven-Zven receptor binding causes mobilization of Ca^{2+}. Rather Sheppard provides a laundry list of metabolic events that are "often linked to receptor-ligand interactions." Applicants note that Sheppard uses the term "often" not "always." The list of metabolic events that are often, but not always, associated with ligand-receptor interactions include gene transcription, phosphorylation, dephosphorylation, increases in cyclic AMP production, mobilization of cellular calcium, mobilization of membrane lipids, cell adhesion, hydrolysis of inositol lipids and hydrolysis of phospholipids. See Sheppard, col. 10, lines 58-63. Nowhere does Sheppard teach or suggest that either Zven binding to a Zven receptor gives rise to Ca^{2+} mobilization. At best Sheppard indicates that calcium ion mobilization is one possible metabolic event that might arise from Zven binding to a Zven receptor. Given the multifarious possibilities that Sheppard gives for possible ligand-receptor binding- associated metabolic events, the person having ordinary skill in the art would not have been motivated to contact a preparation comprising prokineticin receptor and a calcium ion indicator with a candidate compound and to measure a calcium ion indicator signal to identify a prokineticin receptor ligand.

Sheppard simply fails to provide the specific teaching or suggestion that Zven binding to a Zven receptor gives rise to calcium ion signal, which would be necessary to render the pending claims obvious.

The Costanzo reference does not provide the missing teaching of detecting a calcium indicator signal to identify a prokineticin receptor ligand. At best, the Costanzo reference teaches that depolarization of smooth muscle cell membrane opens voltage-dependent Ca^{2+} channels so that calcium ions flow into the cell and down its electrochemical gradient, increasing intracellular calcium ion concentration. Costanzo does not teach that Zven-Zven receptor binding causes depolarization of smooth muscle cell membrane. As discussed above with respect to Sheppard, there are multiple possible causes of smooth muscle cell depolarization, and calcium mobilization is but one of many possible metabolic consequences of Zven-Zven receptor binding known to the person of ordinary skill in art at the time of the present invention. Thus, Costanzo fails to provide the missing teaching of Sheppard that would have been necessary for the person of ordinary skill in the art to complete the claimed invention.

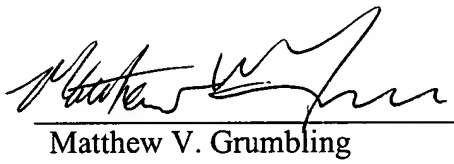
Given the state of the art at the time that the present inventors invented the claimed methods, the person of ordinary skill in the art would have envisioned multiple possible metabolic consequences of Zven-Zven receptor binding that might give rise to a cognizable signal. A person having ordinary skill in the art would have been just as likely to be led by Sheppard to look for potassium or chloride ion channel activity, or some other metabolically significant activity, as a consequence of Zven-Zven receptor binding. Whatever Costanzo might teach to one of ordinary skill in the art about smooth muscle cell contractility in general, the reference fails to solve the mystery posed by Sheppard of how Zven interacts with its receptor to give rise to contractility. Thus neither reference, neither in isolation nor in combination, could have led the person of ordinary skill in the art to practice the claimed methods with a reasonable expectation of success. Accordingly, Applicants submit that a rejection of the pending claims under § 103(a) over a combination of Sheppard and Costanzo would be untenable.

In view of the foregoing, Applicants submit that a rejection of the pending claims under § 103(a) over a combination of Sheppard and Costanzo would be untenable.

CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that claims 42 and 91-96 are now in condition for allowance and respectfully request a notice to this effect. Should there be any questions or suggestions for expediting allowance, Applicants invite the Examiner to call the undersigned attorney at the telephone number below.

Respectfully submitted,



Dated: July 12, 2004

Matthew V. Grumbling
Registration No. 44,427
Telephone No.: (858) 535-9001
Facsimile No.: (858) 535-8949

McDERMOTT WILL & EMERY LLP
4370 La Jolla Village Drive, Suite 700
San Diego, California 92122

Enclosures: 9 references